#17

Patent Case No. WW-0041A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Bristol-Myers Squibb Company
U. S. Patent No.:	5,194,247
Issue Date:	March 16, 1993
For:	Synergistic Skin Depigmentation Composition
Inventors:	Xina Nair, Kenneth Tramposch

APPLICATION FOR EXTENSION OF PATENT TERM
UNDER 35 USC 156

Honorable Commissioner of
Patents and Trademarks
Washington, D. C. 20231

Dear Sir:

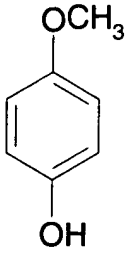
In accordance with the provisions of 35 USC 156, Bristol-Myers Squibb Company, a corporation of the state of Delaware, having a place of business at 345 Park Avenue, New York, New York, 10154, hereby applies for an extension of 1365 days of the term of United States Patent No. 5,194,247 issued March 16, 1993, from an expiration date of March 16, 2010 to December 10, 2013.

The following items are relevant and follow the guidelines set forth by the United States Patent and Trademark Office Rules of Practice; 37 CFR §1.710, et seq.

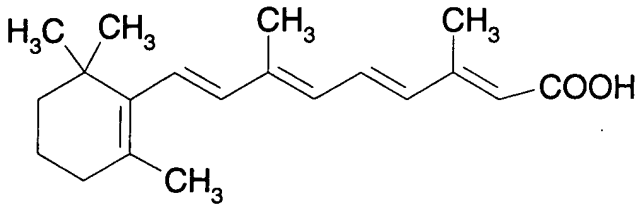
03/07/2000 00000009 2 111 $1,120.00 03/03/2000 DA 193880

1) This application for extension is based upon the regulatory review period before the Food and Drug Administration of SOLAGE®. SOLAGE is the trademark of Bristol-Myers Squibb Company for a dermatological drug product having as its active ingredients mequinol and tretinoin in topical solution. The package insert for SOLAGE is enclosed herewith as Appendix 1.

Mequinol is designated chemically as 4-hydroxyanisole (also referred to as 1-hydroxy-4-methoxybenzene), and has the following structure:



Tretinoin is designated chemically as (all E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid (also referred to as all-trans-retinoic acid), and has the following structure:



2) SOLAGE received permission for commercial marketing and use under Section 505 of the Federal Food, Drug and Cosmetic Act on December 10, 1999, for the treatment of solar lentigines.

3) Regulatory review of SOLAGE occurred under Section 505 of the Federal Food, Drug and Cosmetic Act (21 USC 355).

4) Mequinol and tretinoin are the only active ingredients in SOLAGE. The combination of mequinol and tretinoin has not been approved previously for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act. Mequinol has not been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act. Tretinoin (all-trans retinoic acid) was approved October 20, 1971 under Section 505(b) of the Federal Food, Drug and Cosmetic Act for the treatment of acne (NDA 16921 for Retin-A).

5) This application for extension of the term of United States Patent No. 5,194,247 is being submitted within the 60 day period permitted for submission pursuant to 37 CFR §1.720(f) beginning on December 10, 1999. The last day on which the application could be submitted is February 8, 2000.

6) This application for extension of patent term seeks to extend the term of United States Patent No. 5,194,247 issued March 16, 1993, which unless extended will expire on March 16, 2010, under provisions of the recently enacted Uruguay Round Agreements Act. This patent has <u>not</u> previously been extended.

The inventors named in the patent are Xina Nair and Kenneth Tramposch. The patent is owned by Bristol-Myers Squibb Company by means of an assignment to its predecessor, Bristol-Myers Company. The pertinent assignment was recorded on July 30, 1990 in the United States Patent and Trademark Office at Reel 5395, Frame 0273.

7) Attached hereto as Appendix 2 is a copy of United States Patent No. 5,194,247.

8) No disclaimers, certificates of correction, or reexamination certificates have been filed or issued in United States Patent No. 5,194,247. Copy of receipt for year four maintenance fee payment to the USPTO is attached as Appendix 3.

9) United States Patent No. 5,194,247 claims compositions containing the mixture of mequinol and tretinoin, the active ingredients in SOLAGE, which contains 2% w/v mequinol (4-hydroxyanisole) and 0.01% w/v tretinoin (all-trans retinoic acid). The package insert for SOLAGE shows that it is an aqueous solution in plastic bottles having an applicator, for dermatological (external) application. SOLAGE is approved in plastic bottles having an applicator containing 30mL SOLAGE solution, which solution contains the ingredients in the table below:

Ingredient	% Label	Kg/100L[1]	Function
4-Hydroxyanisole (BMS-181158)	2.0 (w/v)	2.05[2]	Active Ingredient
Tretinoin, USP (BMS-181159)	0.01 (w/v)	0.0120[3]	Active Ingredient
Ethyl Alcohol, USP	77.8 (v/v)	64.20[4]	Solvent, vehicle
PEG-8 (Polyethylene Glycol 400, NF)	3.9 (v/v)	4.40[5]	Solvent, humectant
Butylated Hydroxytoluene, NF (BHT)	0.088 (w/v)	0.088	Antioxidant
Ascorbic Acid, USP	0.044 (w/v)	0.044	Antioxidant
Citric Acid, USP	0.088 (w/v)	0.088	Chelating agent
Ascorbyl Palmitate, NF	0.044 (w/v)	0.044	Antioxidant

Disodium EDTA, USP	0.044 (w/v)	0.044	Chelating agent
Water for Production (Purified Water, USP	18.5 (v/v)	18.5	Vehicle

1. A 100 L batch is the equivalent of 87.9 Kg without manufacturing overages
2. A 2.5% overage is used to compensate for degrading during storage
3. A 20% overage is used to compensate for degradation during storage
4. A 2% overage is used to compensate for losses during manufacturing
5. The specific gravity of PEG-8 is 1.1254.

Claims 1-3 cover pharmaceutical compositions for skin depigmentation free of a corticosteriod, which consist essentially of mequinol (4-hydroxyanisole) and tretinoin (all-trans retinoic acid). Claims 10-12 cover methods for depigmenting skin using compositions free of a corticosteroid, which consist essentially of mequinol (4-hydroxyanisole) and tretinoin (all-trans retinoic acid).

Solar lentigines are localized, pigmented, macular lesions. Treatment of the affected area of the skin lightens (depigments) the lesion.

A description of Claims 1-3 and 10-12 of U. S. Patent No. 5,194,247 follows.

Claim 1 of U. S. Patent No. 5,194,247 covers a pharmaceutical composition for depigmenting skin, which does not contain a corticosteroid, and which consists essentially of 0.1% to 5% by weight 4-hydroxyanisole (mequinol) and 0.001% to 1% by weight of at least one retinoid including all-trans retinoic acid (tretinoin), in a pharmaceutically acceptable topical vehicle.

Claim 2 is dependent on Claim 1 and covers the composition when the retinoid is all-trans retinoic acid (tretinoin).

Claim 3 is dependent on Claim 2 and covers the composition containing from 1 to 2% by weight 4-hydroxyanisole and 0.01 to 0.1% by weight all-trans retinoic acid.

Claim 10 covers a method for depigmenting skin comprising topically applying to the skin a synergistic composition that does not contain a corticosteroid consisting essentially of 0.1% to 5% by weight 4-hydroxyanisole (mequinol) and 0.001% to 1% by weight of at least one retinoid including all-trans retinoic acid (tretinoin).

Claim 11 is dependent on Claim 10 and covers the method when the retinoid is all-trans retinoic acid (tretinoin).

Claim 12 is dependent on Claim 10 and covers the method when the composition contains 1% to 2% by weight 4-hydroxyanisole (mequinol) and 0.01% to 0.1% by weight all-trans retinoic acid (tretinoin).

10) The relevant dates and information pursuant to 35 USC 156(g) that will enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

For 35 USC 156(g)(1)(B)(i)-

The Notice of Claimed Investigational Exemption for a New Drug (IND number 40,038) for 2% 4-hydroxyanisole/0.01% tretinoin, under the provisions of Section 505(I) of the Federal Food, Drug and Cosmetic Act, was filed on June 30, 1992, amended December 27, 1993, and became effective on August 3, 1992.

The New Drug Application (number 20-922) for SOLAGE, under Section 505(b) of the Federal Food, Drug and Cosmetic Act, was filed on December 30, 1997.

For 35 USC 156(g)(1)(B)(ii)-

The New Drug Application (number 20-922) for SOLAGE, under Section 505(b) of the Federal Food, Drug and Cosmetic Act, was filed on December 30, 1997.

The New Drug Application (number 20-922) for SOLAGE, under Section 505(b) of the Federal Food, Drug and Cosmetic Act, was approved on December 10, 1999.

11) The following is a brief description of certain significant activities undertaken by Bristol-Myers Squibb Company during the applicable regulatory review period with respect to SOLAGE including the dates applicable to such activities. Continuing from the date of the first use in humans through the time of FDA approval, there were clinical studies in progress and/or being planned, with regular and frequent communications between Bristol-Myers Squibb Company and the FDA, and between Bristol-Myers Squibb Company and its clinical investigators.

June 30, 1992	Investigational New Drug Application 40,038 filed.
August 3, 1992	IND is effective.
August 7, 1993	Clinical tests commence.
November 29, 1993	Protocols for the 12 month photocarcinogenicity study and the 24 month dermal study were submitted for review.
December 27, 1993	An IND amendment was submitted providing the final report from the segment II dermal teratology study in rabbits.
April 14, 1994	End-of-Phase II meeting held with the FDA to discuss the further clinical development of Mequinol/Tretinoin.
June 2, 1994	IND amendment submitted providing the rationale for the need of 25% average of Tretinoin.
October 20, 1994	IND amendment submitted regarding efficacy criterion for the pivotal studies.
November 30, 1994	Discussions with FDA regarding additional mutagenicity studies.
April 10, 1995	Meeting with FDA, which requested study to correlate improvement with subject's ability to attain goals.

March 6, 1996	IND amendment submitted with results of improvement level study requested April 10, 1995 by FDA.
May 1, 1996	List of drug safety studies submitted to FDA
July 1, 1996	Discussions with FDA regarding efficacy measures.
August 22, 1996	IND amendment submitted regarding questions from FDA.
September 16, 1996	Discussions in which BMS agreed to conduct two dose range-finding studies.
December 19, 1996	IND amendment submitted with results from range-finding studies.
November 11, 1997	IND annual report submitted to FDA.
December 30, 1997	New Drug Application for 2% Mequinol/0.01% Tretinoin Topical Solution submitted.
July 16, 1998	Westwood-Squibb (Buffalo) site found acceptable following response to FDA inspection findings.
August 11, 1998	FDA requests method validation samples.
December 11, 1998	Addition of Nycomed as alternate supplier of 4-hydroxyanisole (mequinol).
December 23, 1998	FDA issues information request letter with review comments.
February 5, 1999	Response to 12/23 information request letter, including mock up of artwork.
February 10, 1999	Information on dimethoxybenzone safety submitted to FDA.
March 3, 1999	Discussion of halo hypopigmentation with FDA.

March 5, 1999	Proposed patient-directed labeling submitted to FDA.
March 9, 1999	Advance Materials for teleconference submitted to FDA.
March 25, 1999	Rationale to support request for Category C labeling submitted to FDA.
March 26, 1999	FDA requested phase IV commitments.
March 26, 1999	Revised draft package insert.
March 30, 1999	Approvable letter submitted to FDA.
June 15, 1999	Request for meeting with FDA by Bristol-Myers Squibb Company.
November 15, 1999	Acceptance of approvable letter by FDA.
December 10, 1999	NDA approved.

12) It is the opinion of Bristol-Myers Squibb Company that United States No.5,194,247 is eligible for an extension of its term of 1365 days since:

(a) It claims the pharmaceutical composition 2% Mequinol/0.01% Tretinoin in the approved human drug product SOLAGE and a method for using same;

(b) The term of said patent has never been previously extended;

(c) The application for extension of patent term is submitted by the owner of the patent, Bristol-Myers Squibb Company;

(d) The product, SOLAGE, has been subject to regulatory review prior to commercial marketing or use;

(e) The product received permission for commercial marketing or use on December 10, 1999 and the application for patent term extension has been submitted within 60 days from that date;

(f) The term of the patent has not expired prior to this date of application; and

(g) No other patent term has been extended for the same regulatory review period for this product.

The length of extension claimed was determined in accordance with 35 USC §156(g) and 37 CFR§1.775(d). Since the subject patent, United States Patent No.5,194,247 was issued after the 1984 enactment of §156 and the clinical investigation under IND 40,038 also commenced after the 1984 enactment date, the period of extension based on the regulatory review may not exceed five years, nor may the patent be extended beyond fourteen years after the NDA approval date.

The total extension time comprises the sum total of days of the testing and approval periods, less one-half of the days in the testing period. In the present case, the pertinent dates are:

Patent issued:	March 16, 1993
Testing period began:	August 3, 1992
NDA submitted:	December 30, 1997
NDA approved:	December 10, 1999

Calculation of the total extension time pursuant to 37 CFR §1.775(d)(4) yields 1715 days according to the formula:

$$[2685\ (\text{number of days from IND to NDA approval}) - 988\ (\text{one half number of days from IND to NDA submission})] = 1697\ \text{Days}$$

However, 37 CFR §1.775(d)(4) applies and provides a maximum extension period limited to fourteen years from NDA approval. Since it is the earlier date to be applied, the extension period being sought is limited by this fourteen year period to December 10, 2013 or 1365 days.

13) Bristol-Myers Squibb Company and the undersigned acknowledge a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information that is material to the determination of entitlement to the extension sought.

14) Authorization in accordance with 37 CFR §1.20(j) is given to charge the One Thousand One Hundred and Twenty Dollars ($1,120.00) fee for receiving and acting upon the application for extension to Deposit Account No. 193880. In the event the actual fee differs from this amount, it is requested that the overpayment or under payment be credited or charged to Deposit Account No. 193880.

15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to this application for patent term extension should be directed is:

Charles J. Zeller
Bristol-Myers Squibb Company
2 Blachley Road
Stamford, CT 06922
Phone: (203) 316-2566

16) A duplicate copy of this application, certified as such, is enclosed.

17) A signed declaration by a representative of Bristol-Myers Squibb Company is submitted herewith in compliance with 37 CFR 1.740(a)(17).

Respectfully submitted,

Dated: February 4, 2000

Charles J. Zeller
Registration No. 28,682
Attorney for Applicants
Bristol-Myers Squibb Company
2 Blachley Road
Stamford, CT 06922

Patent Case No. WW-0041A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Bristol-Myers Squibb Company
U. S. Patent No.:	5,194,247
Issue Date:	March 16, 1993
For:	Synergistic Skin Depigmentation Composition
Inventors:	Xina Nair, Kenneth Tramposch

DECLARATION IN ACCORDANCE WITH 37 CFR§1.740(B)

Honorable Commissioner of
Patents and Trademarks
Washington, D. C. 20231

Dear Sir:

I, Charles J. Zeller, residing at Riverdale, New York, declare as follows:

1. That I am an Associate Patent Counsel of Bristol-Myers Squibb Company, a corporation of the state of Delaware, having a place of business at 2 Blachley Road, Stamford, Connecticut 06922; I am an attorney registered to practice in the United States Patent and Trademark Office under registration no. 28, 682 and I have general authority from Bristol-Myers Squibb Company to act on its behalf in patent matters.

2. That Bristol-Myers Squibb Company is the owner of the entire right, title and interest in United States Patent No. 5,194,247.

3. That I have reviewed and understand the contents of the Application for Extension of Patent Term Under 35 USC 156 for United States Patent No. 5,194,247 which is submitted herewith.

4. That I believe that the above-identified patent is subject to an extension pursuant to 37 CFR§1.710.

5. That I believe that an extension of the term of the patent of 1365 days is fully justified under 35USC156 and the applicable regulations.

6. That I believe that the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37CFR§1,720.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application for extension of patent term and the validity of United States Patent No. 5,194,247.

Respectfully submitted,

Dated: February 4, 2000

Charles J. Zeller
Registration No. 28,682
Attorney for Applicants
Bristol-Myers Squibb Company
2 Blachley Road
Stamford, CT 06922
Phone: (203) 316-2566

US PATENT 5194247

APPLICATION FOR EXTENSION OF PATENT TERM
UNDER 35 USC 156

APPENDIX 1

PHARMACOKINETICS:

The percutaneous absorption of tretinoin and the systemic exposure to tretinoin and mequinol were assessed in healthy subjects (n=8) following two weeks of twice daily topical treatment of Solagé. Approximately 0.8 mL of Solagé was applied to a 400 cm^2 area of the back, corresponding to a dose of 37.3 $\mu g/cm^2$ for mequinol and 0.23 $\mu g/cm^2$ for tretinoin. The percutaneous absorption of tretinoin was approximately 4.4%, and systemic concentrations did not increase over endogenous levels. The mean C_{max} for mequinol was 9.92 ng/mL (range 4.22 to 23.62 ng/mL) and the T_{max} was 2 hours (range 1 to 2 hours).

INDICATIONS AND USAGE:

(To understand fully the indication for this product, please read the entire INDICATIONS AND USAGE section of the labeling).

Solagé (mequinol, 2%, tretinoin, 0.01%) Topical Solution is indicated for the treatment of solar lentigines.

Solagé should only be used under medical supervision as an adjunct to a comprehensive skin care and sun avoidance program where the patient should primarily either avoid the sun or use protective clothing.

Neither the safety nor effectiveness of Solagé for the prevention or treatment of melasma or postinflammatory hyperpigmentation has been established.

The efficacy of using Solagé daily for greater than 24 weeks has not been established.

The local cutaneous safety of using Solagé in non-Caucasians has not been adequately established (see **CLINICAL STUDIES** section).

CONTRAINDICATIONS: The combination of mequinol and tretinoin may cause fetal harm when administered to a pregnant woman. Due to the known effects of these active ingredients, Solagé Topical Solution should not be used in women of childbearing potential.

In a dermal teratology study in New Zealand White rabbits, there were no statistically significant differences among treatment groups in fetal malformation data; however, marked hydrocephaly with visible doming of the head was observed in one mid-dose litter (12 and 0.06 mg/kg or 132 and 0.66 mg/m^2 of mequinol and tretinoin, respectively) and two fetuses in one high dose litter (40 and 0.2 mg/kg or 440 and 2.2 mg/m^2 of mequinol and tretinoin, respectively) of Solagé, and two high-dose tretinoin (0.2 mg/kg, 2.2 mg/m^2) treated litters. These malformations were considered to be treatment related and due to the known effects of tretinoin. This was further supported by coincident appearance of other malformations associated with tretinoin, such as cleft palate and appendicular skeletal defects. No effects attributed to treatment were observed in rabbits in that study treated topically with mequinol alone (dose 40 mg/kg, 440 mg/m^2). A no-

observed-effect level (NOEL) for teratogenicity in rabbits was established at 4 and 0.02 mg/kg (44 and 0.22 mg/m^2 mequinol and tretinoin, respectively) for Solagé, which is approximately the maximum possible human daily dose, based on clinical application to 5% of total body surface area. Plasma tretinoin concentrations were not raised above endogenous levels, even at teratogenic doses. Plasma mequinol concentrations in rabbits at the NOEL at one hour after application were 124 ng/mL or approximately twelve times the mean peak plasma concentrations of that substance seen in human subjects in a clinical pharmacokinetic study.

In a repeated study in pregnant rabbits administered the same dose levels as the study described above, additional precautionary measures were taken to prevent ingestion, although there is no evidence to confirm that ingestion occurred in the initial study. Precautionary measures additionally limited transdermal absorption to a six hour exposure period, or approximately one-fourth of the human clinical daily continuous exposure time. This study did not show any significant teratogenic effects at doses up to approximately 13 times the human dose on a mg/m^2 basis. However, a concurrent tretinoin dose group (0.2 mg/kg/day) did include two litters with limb malformations.

In a published study in albino rats (J. Am. Coll. Toxicology 4(5):31-63, 1985), topical application of 5% mequinol in a cream vehicle during gestation was embryotoxic and embryolethal. Embryonic loss prior to implantation was noted in that study where animals were treated throughout gestation. Coincidentally, mean preimplantation embryonic loss was increased in the first rabbit study in all mequinol treated groups, relative to control, and in the high dose mequinol/tretinoin and tretinoin only treated groups in the second study. In those studies, dosing began at gestation day 6, when implantation is purported to occur. Increased preimplantation loss was also noted at the high combination dose in a study of early embryonic effects in rats, as was decreased body weight in male pups; these findings are consistent with the published study.

Solagé was not teratogenic in Sprague-Dawley rats when given in topical doses of 80 and 0.4 mg/kg mequinol and tretinoin, respectively (480 and 2.4 mg/m^2 or 11 times the maximum human daily dose). The maximum human dose is defined as the amount of solution applied daily to 5% of the total body surface area.

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty cases of temporally-associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin. Although no definite pattern of teratogenicity and no causal association has been established from these cases, 6 of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

No adequate or well-controlled trials have been conducted with Solagé in pregnant women.

Solagé Topical Solution is contraindicated in individuals with a history of sensitivity reactions to any of its ingredients. It should be discontinued if hypersensitivity to any of its ingredients is noted.

WARNINGS:

Solagé is a dermal irritant and the results of continued irritation of the skin for greater than 52 weeks in chronic, long-term use are not known. Tretinoin has been reported to cause severe irritation on eczematous skin and should be used only with utmost caution in patients with this condition.

Safety and effectiveness of Solagé in individuals with moderately or heavily pigmented skin have not been established.

Solagé should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) to treated areas should be avoided or minimized during the use of Solagé. Patients must be advised to use protective clothing and comply with a comprehensive sun avoidance program when using Solagé. Data are not available to establish how or whether Solagé is degraded (either by sunlight or by normal interior lighting) following application to the skin. Patients with sunburn should be advised not to use Solagé until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using Solagé and ensure that the precautions outlined in the Patient Medication Guide are observed.

Solagé should be kept out of the eyes, mouth, paranasal creases, and mucous membranes. Solagé may cause skin irritation, erythema, burning, stinging or tingling, peeling, and pruritus. If the degree of such local irritation warrants, patients should be directed to use less medication, decrease the frequency of application, discontinue use temporarily, or discontinue use altogether. The efficacy at reduced frequencies of application has not been established.

Solagé should be used with caution by patients with a history, or family history, of vitiligo. One patient in the trials, whose brother had vitiligo, experienced hypopigmentation in areas that had not been treated with study medication. Some of these areas continued to worsen for at least one month post treatment with Solagé. Six weeks later the severity of the hypopigmentation had decreased from moderate to mild and 106 days post treatment, the patient had resolution of some but not all lesions.

Application of larger amounts of medication than recommended will not lead to more rapid or better results, and marked redness, peeling, discomfort, or hypopigmentation of the skin may occur.

PRECAUTIONS

General: For external use only.
Solagé should only be used as an adjunct to a comprehensive skin care and sun avoidance program (See **INDICATIONS AND USAGE** section).

If a drug sensitivity, chemical irritation, or a systemic adverse reaction develops, use of Solagé should be discontinued.

Weather extremes, such as wind or cold, may be more irritating to patients using Solagé.

Information for patients: Patients require detailed instruction to obtain maximal benefits and to understand all the precautions necessary to use this product with greatest safety. The Patient Medication Guide is attached to this Package Insert.

Drug Interactions: Concomitant topical products with a strong skin drying effect, products with high concentrations of alcohol, astringents, spices or lime, medicated soaps or shampoos, permanent wave solutions, electrolysis, hair depilatories or waxes, or other preparations that might dry or irritate the skin should be used with caution in patients being treated with Solagé because they may increase irritation when used with Solagé.

Solagé should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although a dermal carcinogenicity study in CD-1 mice indicated that Solagé applied topically at daily doses up to 80 and 0.4 mg/kg (240 and 1.2 mg/m^2) of mequinol and tretinoin, respectively, representing approximately 5 times the maximum possible systemic human exposure was not carcinogenic, in a photocarcinogenicity study utilizing Crl:Skh-1(hr/hr BR) hairless albino mice, median time to onset of tumors decreased. Also, the number of tumors increased in all dose groups administered 1.4, 4.3, or 14 μl of Solagé/cm^2 of skin (24 and 0.12, 72 and 0.36, or 240 and 1.2 mg/m^2 of mequinol and tretinoin, respectively; 0.6, 1.9, or 6.5 times the daily human dose on a mg/m^2 basis) following chronic topical dosing with intercurrent exposure to ultraviolet radiation for up to 40 weeks. Similar animal studies have shown an increased tumorigenic risk with the use of retinoids when followed by ultraviolet radiation. Although the significance of these studies to human use is not clear, patients using this product should be advised to avoid or minimize exposure to either sunlight or artificial ultraviolet irradiation sources.

Mequinol was non-mutagenic in the Ames/Salmonella assay using strains TA98, TA100, TA1535, and TA1537, all of which are insensitive to mutagenic effects of structurally-related quinones. Solagé was non-genotoxic in an *in vivo* dermal micronucleus assay in rats, but exposure of bone marrow to drug was not demonstrated.

A dermal reproduction study with Solagé in Sprague-Dawley rats at a daily dose of 80 and 0.4 mg/kg (480 and 2.4 mg/m^2) of mequinol and tretinoin, respectively, approximately 11 times the corresponding maximum possible human exposure, assuming 100% bioavailablity following topical application to 5% of the total body surface area, showed no impairment of fertility.

Pregnancy: Teratogenic effects: Pregnancy Category X. Although the magnitude of the potential for teratogenicity may not be well-defined, Solagé is labeled as an "X" because the potential risk of the use of this drug to treat this particular indication (solar lentigines) in a pregnant woman clearly outweighs any possible benefit (See **CONTRAINDICATIONS** Section).

Nursing mothers: It is not known to what extent mequinol and/or tretinoin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Solagé is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of this product have not been established in pediatric patients. Solagé should not be used on children.

Geriatric Use: Of the total number of patients in clinical studies of Solagé, approximately 43% were 65 and older, while approximately 8% were 75 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients.

ADVERSE REACTIONS

In clinical trials, adverse reactions were primarily mild to moderate in intensity, occurring in 66% and 30% of patients, respectively. The majority of these events were limited to the skin and 64% had an onset of a skin related adverse reaction early in treatment (by week 8). The most frequent adverse reactions in patients treated with Solagé were erythema (49% of patients), burning, stinging or tingling (26%), desquamation (14%), pruritus (12%), and skin irritation (5%).

Some patients experienced temporary hypopigmentation of treated lesions (5%) or of the skin surrounding treated lesions (7%). Ninety-four of 106 patients (89%) had resolution of hypopigmentation upon discontinuation of treatment to the lesion, and/or re-instruction on proper application to the lesion only. Another 8% (9/106) of patients with hypopigmentation events had resolution within 120 days after the end of treatment. Three of the 106 patients (2.8%) had persistence of hypopigmentation beyond 120 days. Approximately 6% of patients discontinued study participation with Solagé due to adverse reactions. These discontinuations were due primarily to skin redness (erythema) or related cutaneous adverse reactions. Solagé was generally well tolerated.

Adverse Events Occurring in >1% of the Population
All Studies

Body System	Solagé (mequinol 2%, tretinoin 0.01%)		Tretinoin, 0.01%		Mequinol, 2%		Vehicle	
	N	%	N	%	N	%	N	%
Skin and Appendages Erythema	421	49.4	261	55.3	13	5.1	8	4.6
Burning/Stinging/Tingling	223	26.1	173	36.7	26	10.2	20	11.4
Desquamation	120	14.1	93	19.7	7	2.8	2	1.1
Pruritus	105	12.3	66	14.0	12	4.7	3	1.7
Halo Hypopigmentation	60	7.0	16	3.4	2	0.8	2	1.1
Hypopigmentation	46	5.4	8	1.7	2	0.8	0	0.0
Irritation Skin	45	5.3	25	5.3	1	0.4	1	0.6
Rash	27	3.2	21	4.4	0	0.0	1	0.6
Skin Dry	27	3.2	18	3.8	3	1.2	1	0.6
Crusting	21	2.5	18	3.8	0	0.0	1	0.6
Rash Vesicular Bullae	18	2.1	8	1.7	0	0.0	0	0.0
Application Site Reaction*	9	1.1	11	2.3	1	0.4	0	0.0

* Events that were considered to be a contact allergic reaction

OVERDOSAGE: If Solagé is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, discomfort, or hypopigmentation may occur. Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of vitamin A (hypervitaminosis A). If oral ingestion occurs, the patient should be monitored, and appropriate supportive measures should be administered as necessary. The maximal no-effect level for oral administration of Solagé in rats was 5.0 mL/kg (30 mg/m^2). Clinical signs observed were attributed to the high alcohol content (77%) of the drug formulation.

DOSAGE AND ADMINISTRATION:

Patients require detailed instruction to obtain maximal benefits and to understand all the precautions necessary to use this product with greatest safety. The physician should review the Patient Medication Guide.

Apply Solagé to the solar lentigines using the applicator tip while avoiding application to the surrounding skin. Use twice daily, morning and evening at least 8 hours apart, or as directed by a physician. Patients should not shower or bathe the treatment areas for at least 6 hours after application of Solagé. Special caution should be taken when applying Solagé to avoid the eyes, mouth, paranasal creases, and mucous membranes.

Application of Solagé may cause transitory stinging, burning or irritation.

Improvement continues gradually through the course of therapy and should be apparent by 24 weeks. Patients should avoid exposure to sunlight (including sunlamps) or wear protective clothing while using Solagé. Data are not available to establish how or whether Solagé is degraded (either by sunlight or by normal interior lighting) following application to the skin.

With discontinuation of Solagé therapy, a majority of patients will experience some repigmentation over time of their lesions.

Applications of larger amounts of medication or more frequently than recommended will not lead to more rapid or better results, and marked redness, peeling, irritation, or hypopigmentation (abnormal lightening) of the skin may occur.

Patients treated with Solagé may use cosmetics but should wait 30 minutes before applying.

Clinical Studies: Two adequate and well-controlled trials evaluated changes in treated hyperpigmented lesions on the face, forearms/back of hands in 421 patients treated with Solagé Topical Solution, 422 patients treated with tretinoin topical solution, 209 patients treated with mequinol topical solution and 107 patients treated with vehicle for up to 24 weeks. In these studies, patients were to avoid sun exposure and use protective clothing, and use of sunscreens was prohibited. Patients were allowed to apply Moisturel® Lotion 30 minutes after application of Solagé. Physicians assessed the extent of improvement or worsening of all the treated lesions from the baseline condition on a 7 point scale. The results of these evaluations are shown below.

	Face		Forearms/Back of Hands	
	Solagé	Vehicle	Solagé	Vehicle
Moderate Improvement or greater[1]	57%	15%	54%	14%
Slight Improvement	28%	36%	26%	33%
No Change[2]	15%	49%	20%	53%

[1]Includes the following grades: Moderate Improvement, Marked Improvement, Almost Clear, Completely Clear. Moderate Improvement or greater was considered clinically meaningful.
[2]Includes the following grades: No Change, Worse (less than 1% of patients treated with Solagé were rated as worse)

Improvement (lightening) of the solar lentigines occurred gradually over time during the 24 week treatment period. At 24 weeks of treatment, 57% and 54% of patients experienced moderate improvement or greater, and 3% and 1% of patients were completely clear of all treated lesions for the face and forearms/back of hands, respectively. It should be noted that approximately 9% of patients, from both treatment areas in these studies, with moderate improvement or greater also experienced hypopigmentation of the skin surrounding at least one treated lesion. There are no vehicle-controlled effectiveness data on the course of lesions treated beyond 24 weeks.

After 24 weeks of treatment, for the forearm/back of hands treatment site, the percentage of patients treated with tretinoin topical solution with moderate improvement or greater, slight improvement, or no change, were 38%, 37%, and 26%, respectively, and for mequinol topical solution were 24%, 40% and 36%, respectively. For the face treatment site, the percentage of patients treated with tretinoin topical solution with moderate improvement or greater, slight improvement, or no change, were 46%, 33%, and 21%, respectively, and for mequinol topical solution were 33%, 30% and 37%, respectively.

The duration of effect was investigated during a period of up to 24 weeks following the discontinuation of treatment. Results from these studies showed that patients may maintain the level of clinical improvement of their treated lesions from the end of treatment through the 24 week follow-up period. However, some degree of repigmentation of treated lesions was observed over time, demonstrating reversibility of the depigmenting action of Solagé.

In the clinical studies, some patients experienced temporary hypopigmentation of treated lesions (5%) or of the skin surrounding treated lesions (7%). Hypopigmentation of the skin surrounding treated lesions occurs even in the setting of proper application of the drug within the lesion border. The majority (94/106 - 89%) resolved upon discontinuation of treatment to the lesion, and/or re-instruction on proper application to the lesion only. Another 8% (9/106) of patients with hypopigmentation events had resolution within 120 days after the end of treatment.

13

Three of the 106 patients (2.8%) had persistence of hypopigmentation beyond 120 days. This further demonstrates the reversibility of the depigmenting action of Solagé.

Over 150 patients used Solagé twice daily for 52 weeks in an open label clinical study. The safety profile for Solagé in this long-term study was similar to that seen in the 24 week studies although burning/stinging/tingling, desquamation, pruritus, and irritation of the skin occurred at lower rates and halo hypopigmentation and hypopigmentation occurred at a slightly greater rate.

Over 90 patients used Solagé twice daily and a concomitant sunscreen (PreSun® 29) daily for up to 24 weeks in an open label clinical study. The safety profile for Solagé in this study was similar to that seen in studies which prohibited sunscreen use although desquamation, pruritus, and halo hypopigmentation occurred at slightly lower rates.

The clinical studies of Solagé included 1794 individuals of Skin Type I - V, 94.5% of whom were Caucasian. The trials also included 5% of individuals who were Asian/Pacific Islander-1.2%, African-American-0.8%, and Hispanic/Latino-3.5%. Safety in Asian/Pacific Islander, African-American, and Hispanic/Latino individuals has not been adequately established. Safety and effectiveness of Solagé in individuals with Skin Type VI (never burns from the sun, deeply pigmented skin) or women of childbearing potential have not been established (see CONTRAINDICATIONS).

HOW SUPPLIED: Solagé is available in 30 mL plastic bottles with an applicator. The bottle should be protected from light by continuing to store in the carton after opening. Store at controlled room temperature, 15-30 °C (59 -86 °F). **Note: FLAMMABLE. Keep away from heat and open flame.**

Buffalo, NY, USA 14213
A Bristol-Myers Squibb Company

Revised March 29, 1999

US PATENT 5194247

APPLICATION FOR EXTENSION OF PATENT TERM
UNDER 35 USC 156

APPENDIX 2

US005194247A

United States Patent [19]

Nair et al.

[11] Patent Number: 5,194,247

[45] Date of Patent: Mar. 16, 1993

[54] SYNERGISTIC SKIN DEPIGMENTATION COMPOSITION

[76] Inventors: Xina Nair, 100 Rolling Meadow, E. Amherst, N.Y. 14051; Kenneth M. Tramposch, 46 Cimarand Dr., Williamsville, N.Y. 14221

[21] Appl. No.: 554,904

[22] Filed: Jul. 24, 1990

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 397,921, Aug. 24, 1989, abandoned.

[51] Int. Cl.[5] A61K 9/00; A61K 31/215

[52] U.S. Cl. 424/59; 424/60; 424/62; 514/171

[58] Field of Search 424/62, 59, 60; 514/171

[56] References Cited

U.S. PATENT DOCUMENTS

3,856,934	12/1974	Kligman	424/62
4,214,000	7/1980	Papa	514/494
4,247,547	1/1981	Marks	514/171

FOREIGN PATENT DOCUMENTS

982945 2/1976 Canada .

Primary Examiner—Thurman K. Page
Assistant Examiner—Amy Hulina

[57] ABSTRACT

There is disclosed a synergistic composition for skin depigmentation with reduced irritation which does not contain a corticosteroid comprising 4-hydroxyanisole and a retinoid, such as all-trans retinoic acid, 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone or (N-acetyl-4-aminophenyl) retinoate, in a pharmaceutically acceptable topical vehicle.

18 Claims, 6 Drawing Sheets

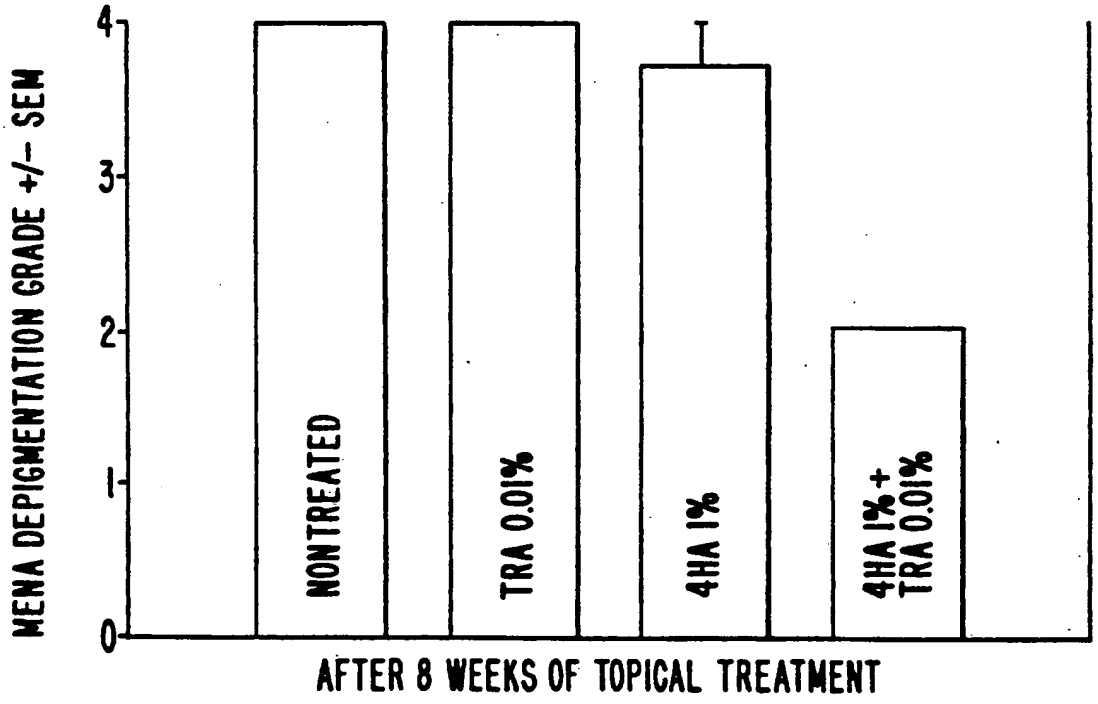


FIG. 1

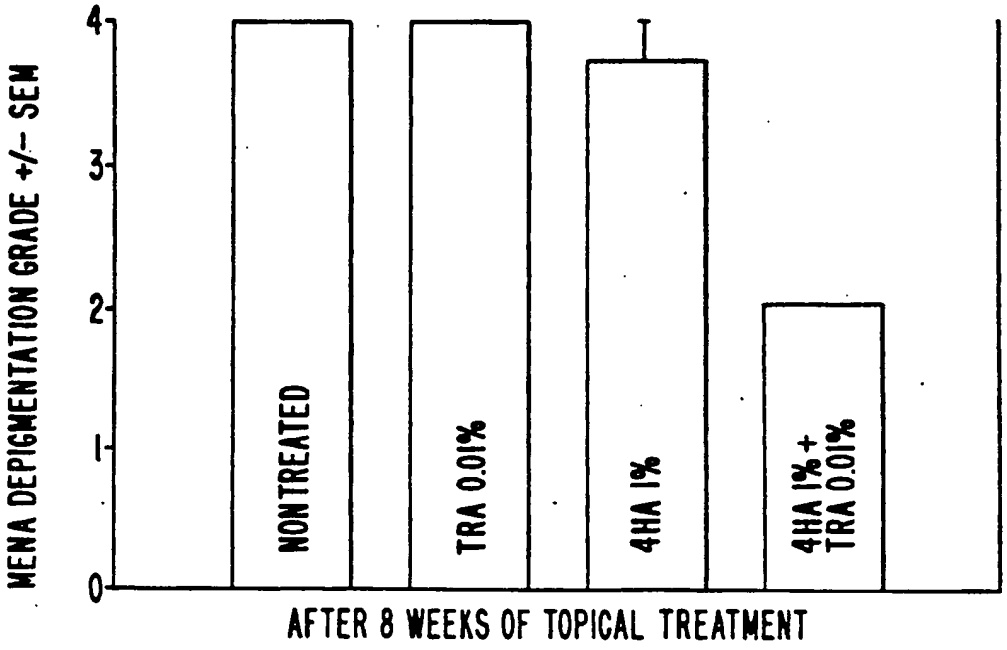

MENA DEPIGMENTATION GRADE +/- SEM
0
1
2
3
4
NONTREATED
TRA 0.01%
4HA 1%
4HA 1% + TRA 0.01%
AFTER 8 WEEKS OF TOPICAL TREATMENT

FIG. 2

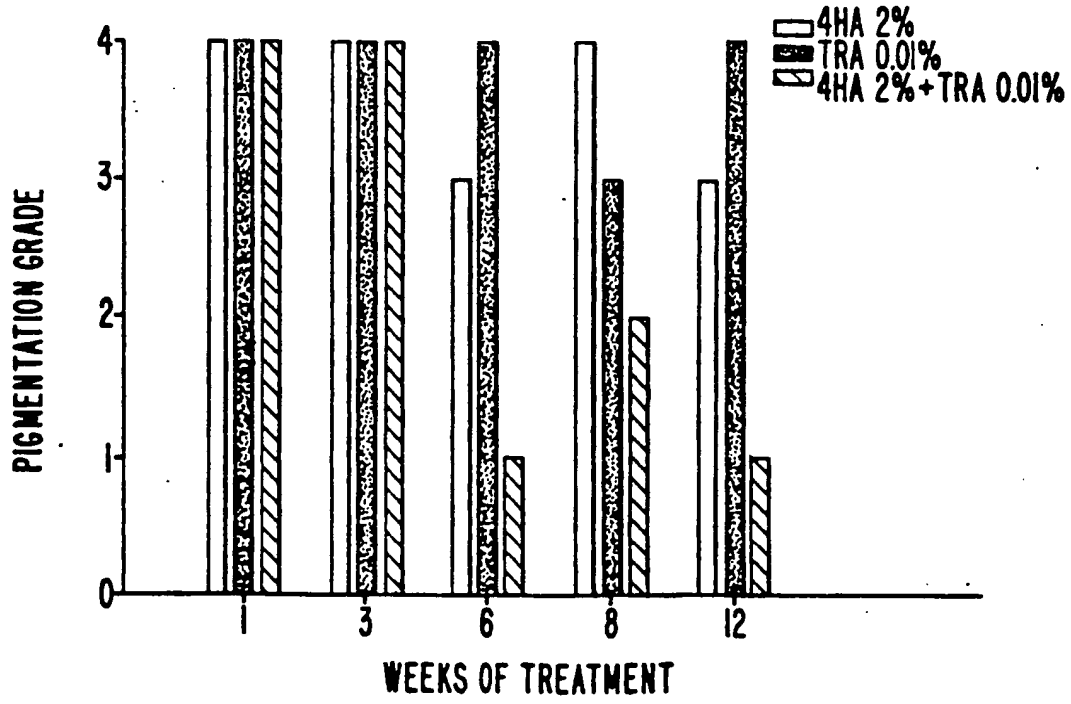

4HA 2%
TRA 0.01%
4HA 2% + TRA 0.01%
PIGMENTATION GRADE
0
1
2
3
4
1
3
6
8
12
WEEKS OF TREATMENT

FIG. 3

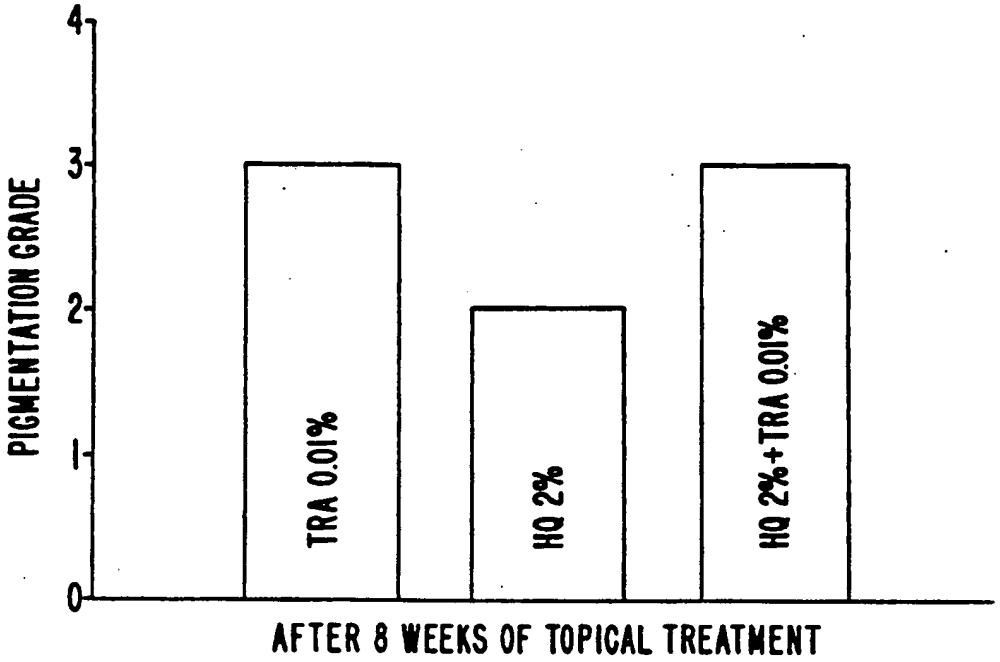

PIGMENTATION GRADE
0
1
2
3
4
TRA 0.01%
HQ 2%
HQ 2%+TRA 0.01%
AFTER 8 WEEKS OF TOPICAL TREATMENT

FIG. 4

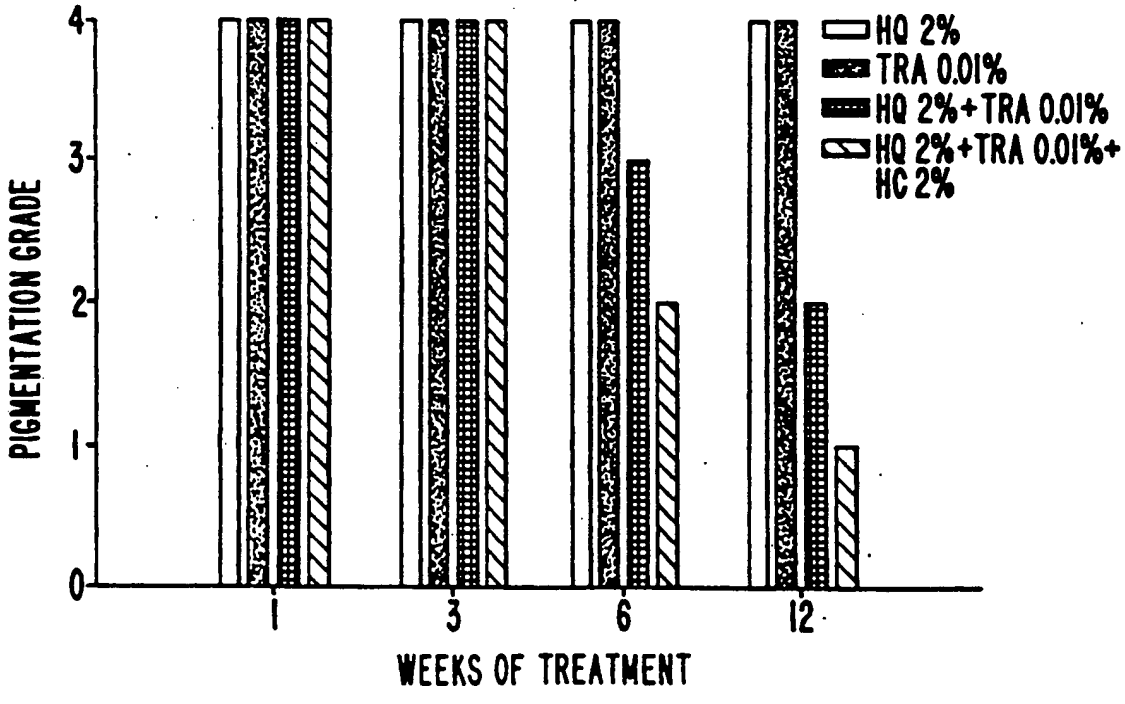

PIGMENTATION GRADE
0
1
2
3
4
1
3
6
12
WEEKS OF TREATMENT
HQ 2%
TRA 0.01%
HQ 2%+TRA 0.01%
HQ 2%+TRA 0.01%+ HC 2%

FIG. 5

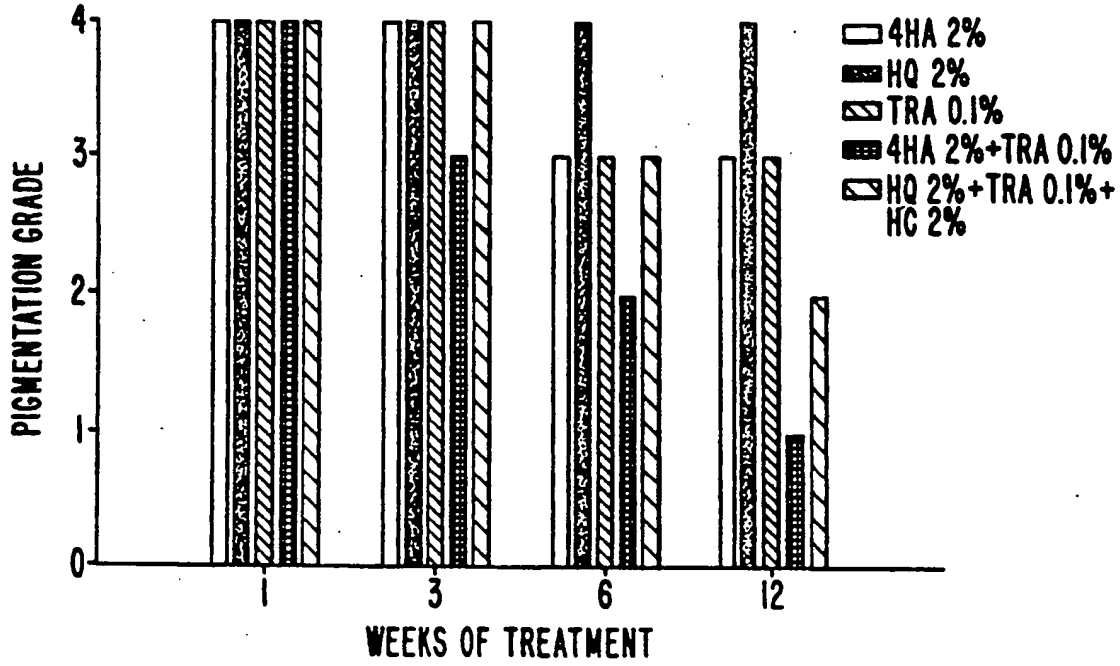

PIGMENTATION GRADE
0
1
2
3
4
1
3
6
12
WEEKS OF TREATMENT
4HA 2%
HQ 2%
TRA 0.1%
4HA 2%+TRA 0.1%
HQ 2%+TRA 0.1%+ HC 2%

FIG. 6

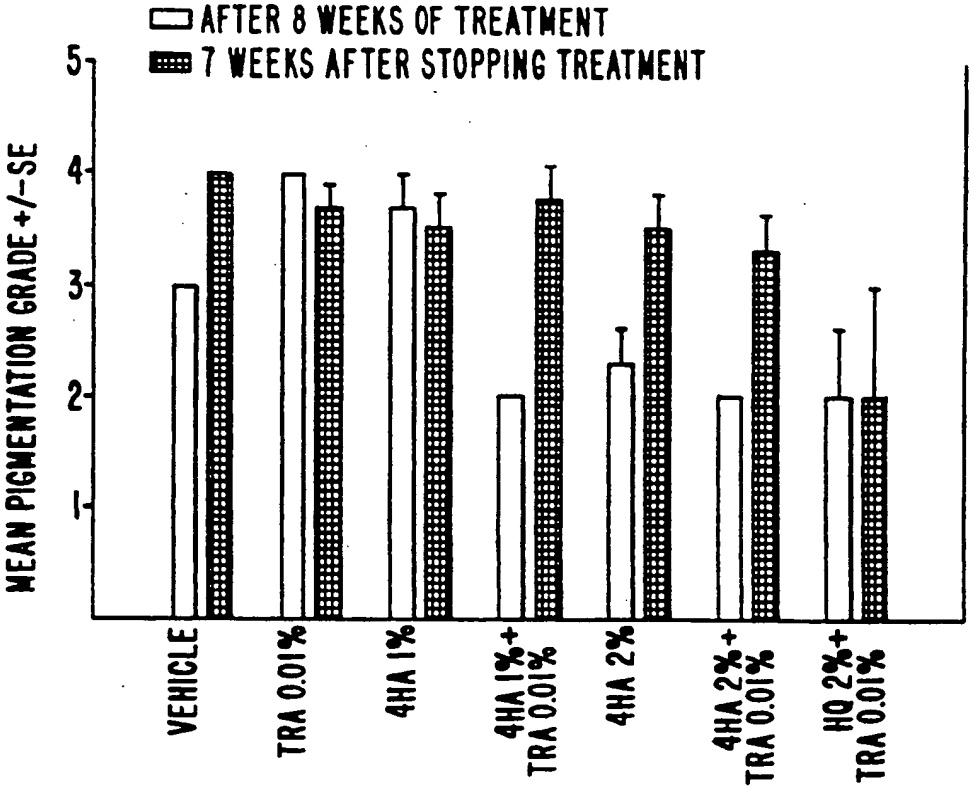
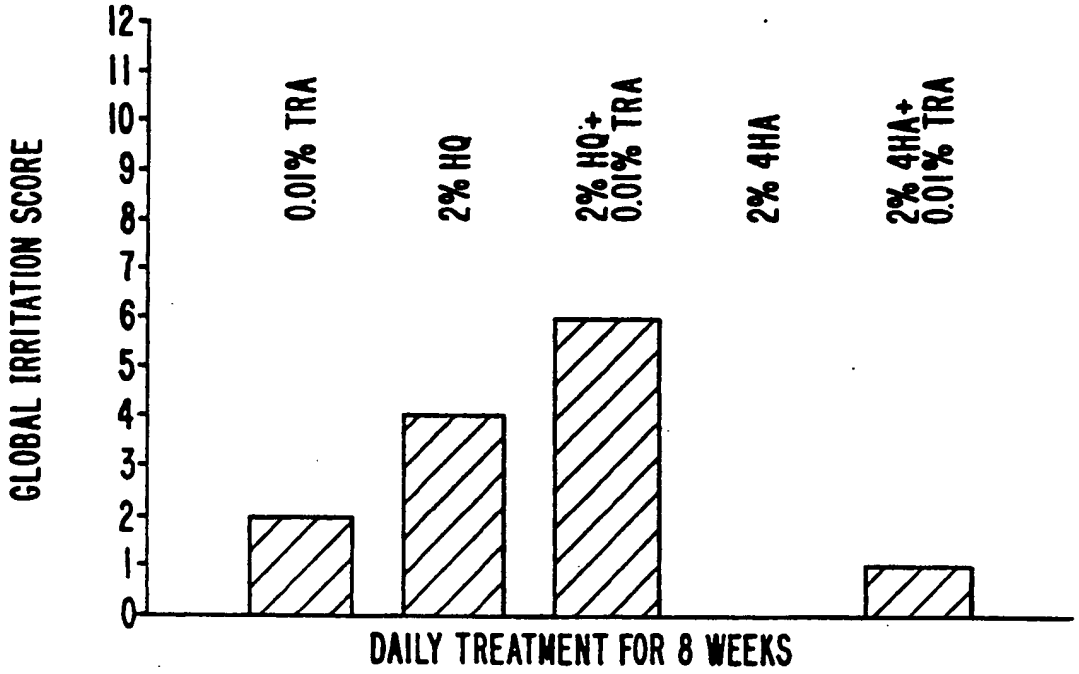

AFTER 8 WEEKS OF TREATMENT
7 WEEKS AFTER STOPPING TREATMENT
MEAN PIGMENTATION GRADE +/-SE
1
2
3
4
5
VEHICLE
TRA 0.01%
4HA 1%
4HA 1%+ TRA 0.01%
4HA 2%
4HA 2%+ TRA 0.01%
HQ 2%+ TRA 0.01%

FIG. 7



SUMMATION OF DRAIZE SCORES FOR ERYTHEMA, EDEMA AND SCALING. 1- MINIMUM EFFECT, 2- SLIGHT EFFECT, 3- MODERATE TO SEVERE EFFECT AND 4- SEVERE EFFECT. THE MAXIMUM ATTAINABLE SCORE - 12.

FIG. 8

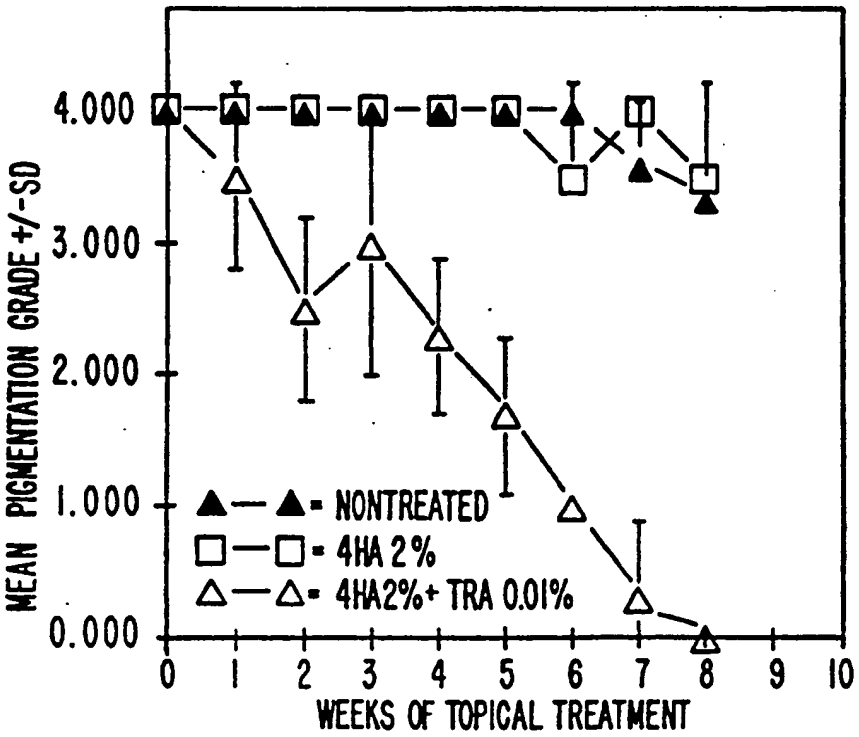

4.000
3.000
2.000
1.000
0.000
MEAN PIGMENTATION GRADE +/-SD
▲—▲= NONTREATED
□—□= 4HA 2%
△—△= 4HA2%+ TRA 0.01%
0 1 2 3 4 5 6 7 8 9 10
WEEKS OF TOPICAL TREATMENT

FIG. 9

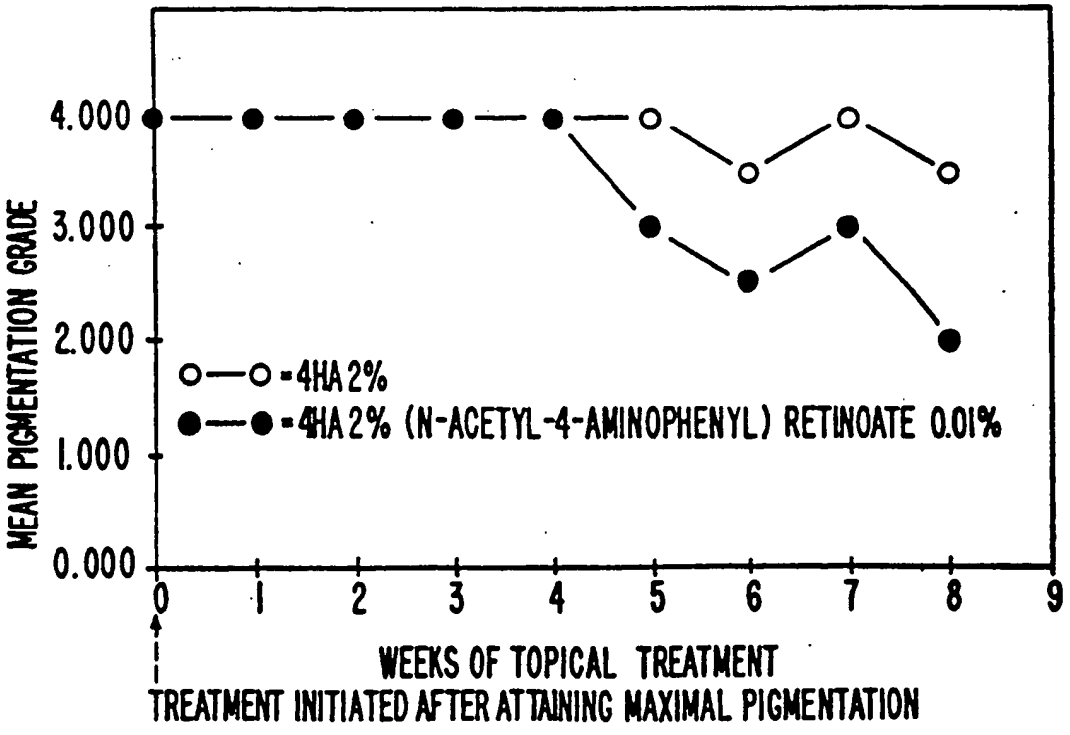
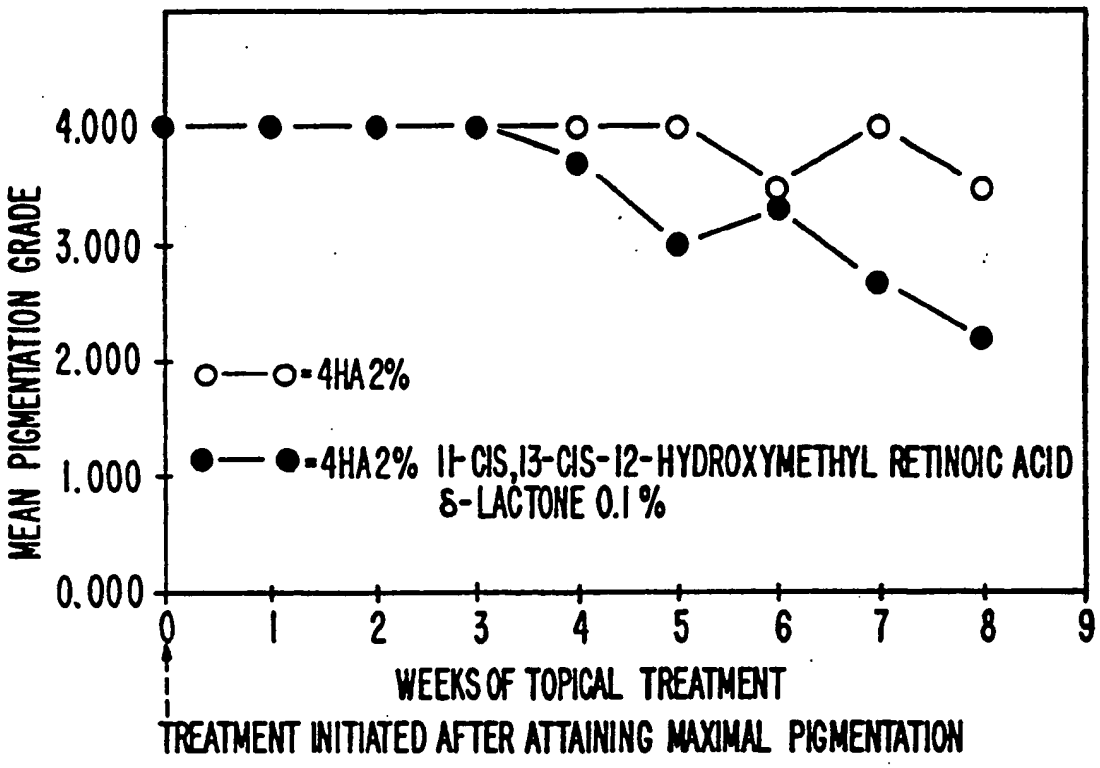

4.000
3.000
2.000
1.000
0.000
MEAN PIGMENTATION GRADE
○—○=4HA 2%
●—●=4HA 2% (N-ACETYL-4-AMINOPHENYL) RETINOATE 0.01%
0 1 2 3 4 5 6 7 8 9
WEEKS OF TOPICAL TREATMENT
TREATMENT INITIATED AFTER ATTAINING MAXIMAL PIGMENTATION

FIG. 10


4.000
3.000
2.000
1.000
0.000
MEAN PIGMENTATION GRADE
o—o=4HA 2%
●—●=4HA 2% 11-CIS,13-CIS-12-HYDROXYMETHYL RETINOIC ACID δ-LACTONE 0.1 %
0
1
2
3
4
5
6
7
8
9
WEEKS OF TOPICAL TREATMENT
TREATMENT INITIATED AFTER ATTAINING MAXIMAL PIGMENTATION

SYNERGISTIC SKIN DEPIGMENTATION COMPOSITION

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of co-pending application Ser. No. 07/397,921, filed Aug. 24, 1989 now abandoned.

BACKGROUND OF THE INVENTION

This invention relates to a synergistic skin depigmentation composition comprising 4-hydroxyanisole and a retinoid such as all-trans retinoic acid, 11-cis, 13-cis-12-hydroxymethyl retinoic acid δ-lactone or (N-acetyl-4-aminophenyl) retinoate.

4-Hydroxyanisole is present as the active ingredient in products used topically for depigmenting or lightening of skin. These products are used in the treatment of hyperpigmentation of skin associated with various skin disorders or diseases. The hyperpigmentation is generally the result of increased melanin deposition in epidermal cells. Hyperpigmentation of skin is associated with freckles, senile lentigo, lentigines, melasma, post-inflammatory hyperpigmentation, sunburn, phototoxic reactions and other conditions. In general, these cases of hyperpigmentation are not life-threatening, but are viewed as cosmetically undesirable and psychologically debilitating.

Local side effects are often associated with the existing products containing greater than 2% hydroquinone or 4-hydroxyanisole. These side effects include localized irritation and irreversible depigmentation. Products containing 2% or less of hydroquinone or 4-hydroxyanisole are generally regarded as ineffective in the treatment of lentigo or melasma.

All-trans retinoic acid (vitamin A acid) applied topically has been reported to lighten the color of lentigo in humans. All-trans retinoic acid is known to increase epidermal cell turnover in normal skin and suppress epidermal cell turnover under stimulated or hyperproliferative conditions. It causes epidermal keratinization and decreases the number of normal cell layers of the stratum corneum. This decrease in thickness of the barrier may potentiate the penetration of other topical agents.

U.S. Pat. No. 3,856,934 and Canadian Patent No. 982,945 disclose a synergistic composition for depigmentation of skin comprising a mixture of hydroquinone, retinoic acid, and a corticosteroid. The U.S. patent also discloses that the double combination of hydroquinone and retinoic acid was not synergistic. Therefore, all three components were needed for the synergistic activity. The Canadian patent discloses that hydroquinone monomethyl ether (4-hydroxyanisole) may be used in the composition instead of hydroquinone. In these patents the corticosteroid is regarded as necessary to bring irritation down to acceptable levels. However, the use of a corticosteroid possesses some disadvantages, i.e., it can be dangerous to use in intertriginous regions, and it may cause skin atrophy, rebound phenomenon and telangiectasia.

BRIEF DESCRIPTION OF THE INVENTION

It has now been discovered that the combination of 4-hydroxyanisole and a retinoid, such as all-trans retinoic acid, 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone or (N-acetyl-4-aminophenyl) retinoate, without the presence of a corticosteroid, results in synergistic depigmentation with diminished irritation of the skin when applied topically in a pharmaceutically acceptable topical vehicle. For example, the combination of 1% by weight of 4-hydroxyanisole and 0.01% by weight of all-trans retinoic acid produced depigmentation of skin that was equivalent to the effect produced by 5% by weight of 4-hydroxyanisole. Individually, 4-hydroxyanisole (1% by weight) and all-trans retinoic acid (0.01% by weight) are without any significant activity. 4-Hydroxyanisole alone at 5% by weight caused depigmentation that was slower to reverse in Yucatan minipigs. The depigmentation produced by the combination of 1% by weight of 4-hydroxyanisole with 0.01% by weight of all-trans retinoic acid showed little or no local irritation, and the depigmentation was reversible in 6-7 weeks after stopping the treatment.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1 and 8 show the synergistic interaction of 1 all-trans retinoic acid and 4-hydroxyanisole.

FIG. 2 shows the synergistic interaction of all-trans retinoic acid and 4-hydroxyanisole over a 12 week period.

FIG. 3 shows the lack of synergism of a composition containing all-trans retinoic acid and hydroquinone.

FIGS. 4 and 5 show the results of various combinations of ingredients.

FIG. 6, shows the reversibility of depigmentation of various compositions.

FIG. 7 shows the irritation effects of various combinations.

FIG. 9 shows the interaction of (N-acetyl-4-aminophenyl) retinoate and 4-hydroxyanisole.

FIG. 10 shows the interaction of all-trans 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone and 4-hydroxy anisole.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect of the present invention, there is provided a synergistic composition for skin depigmentation, which does not contain a corticosteroid, comprising 4-hydroxyanisole and a retinoid, such as all-trans retinoic acid, 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone or (N-acetyl-4-aminophenyl) retinoate, in a pharmaceutically acceptable topical vehicle.

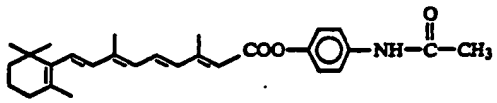
In another aspect, the present invention relates to a method for skin depigmentation comprising topically applying to the skin a combination of 4-hydroxyanisole and a retinoid, such as all-trans retinoic acid, 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone or (N-acetyl-4-aminophenyl) retinoate, in a pharmaceutically acceptable topical vehicle.

A pharmaceutically acceptable topical vehicle into which the 4-hydroxyanisole and retinoid are incorporated may be a cream, gel, ointment, powder, aerosol, emulsion or solution suitable for topical administration. Such topical vehicles are well-known in the art as exemplified by U.S. Pat. No. 4,185,100, the disclosure of which is incorporated herein by reference.

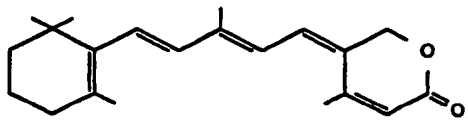
Preferably, the composition of this invention will contain from about 0.1% by weight to about 5% by weight of 4-hydroxyanisole and from about 0.001% by weight to about 1% by weight of all-trans retinoic acid, 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone or (N-acetyl-4-aminophenyl) retinoate. A particularly

preferred composition comprises from about 1% by weight to about 2% by weight of 4-hydroxyanisole and from about 0.01% by weight to about 0.1% by weight of all-trans retinoic acid 11-cis,13-cis-12-hydroxymethyl retinoic acid 6-lactone or (N-acetyl-4-aminophenyl) retinoate.

The compound (N-acetyl-4-aminophenyl) retinoate has the formula:



and the compound 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone has the formula:



IN VIVO EXPERIMENTS

A. Normal Depigmenting Activity

Healthy, female Yucatan minipigs weighing from 25–40 kgms were used in these studies. The animals were selected for even tan to brown skin color. These animals were housed individually in standard stainless steel pens in temperature and humidity controlled rooms with 12-hour cycled lighting. Food was provided at specified times and water was available ad libitum.

Test materials were prepared as solutions in a PEG8-/ethanol vehicle comprising 5 parts by weight of PEG8 (polyethylene glycol 400, a polymer of ethylene oxide that conforms generally to the formula $H(OCH_2CH_2)_nOH$, wherein n has an average value of 8) and 95 parts by weight of ethanol. Test solutions (25 μl) were applied twice daily to a 12.5 cm^2 area of the flank skin five days a week for 8–12 weeks. Test sites were graded at weekly intervals for signs of local irritation and changes in depigmentation using the following grading system:

1=Complete depigmentation
2=Definite uniform depigmentation of test site
3=Small spots of depigmentation
4=Same color as the normal skin

At the end of 8–12 weeks of treatment, selected test sites were biopsied and skin specimens were processed for microscopic examination. The remaining sites were observed for the next 7 weeks for repigmentation or reversibility of depigmentation.

The results of 1% by weight of 4-hydroxyanisole (4HA) combined with 0.01% of all-trans retinoic acid (TRA) are shown in FIG. 1. 4-Hydroxyanisole combined with all-trans retinoic acid showed moderate depigmentation during 6–12 weeks of treatment. Under the same conditions, 4-hydroxyanisole or all-trans retinoic acid alone produced slight to no effect.

FIG. 2 shows that 2% by weight of 4-hydroxyanisole combined with 0.01% by weight of all-trans retinoic acid showed an earlier onset of depigmentation than 4-hydroxyanisole or all-trans retinoic acid alone.

In contrast to the combination of 4-hydroxyanisole and all-trans retinoic acid, 2% by weight of hydroquinone (HQ) combined with 0.01% all-trans retinoic acid was only slightly active and more irritating after eight weeks of treatment, whereas hydroquinone alone was moderately active and all-trans retinoic acid alone was inactive, see FIG. 3. The lower activity with the hydroquinone and all-trans retinoic acid combination is reflective of an increase in pigmentation noted on sites exposed to all-trans retinoic acid. This may be caused by the increased irritation caused by all-trans retinoic acid and hydroquinone.

FIG. 4 shows that 2% by weight of hydroquinone combined with 0.01% by weight of all-trans retinoic acid and 2% by weight of hydrocortisone was comparatively more active than 2% by weight of hydroquinone or 0.01% by weight of all-trans retinoic acid each alone, or a combination of 2% by weight of hydroquinone and 0.01% by weight of all-trans retinoic acid. Hydroquinone combined with all-trans retinoic acid was, in general, less effective than the combination of 4-hydroxyanisole and all-trans retinoic acid.

FIG. 5 shows that 2% by weight of hydroquinone combined with 0.1% by weight of all-trans retinoic acid and 2% by weight of hydrocortisone was less effective than the combination of 2% by weight of 4-hydroxyanisole with 0.1% by weight of all-trans retinoic acid.

The results shown in FIG. 6 again show that the combinations of 1% by weight of 4-hydroxyanisole with 0.01% all-trans retinoic acid applied for eight weeks is active, whereas 1% by weight of 4-hydroxyanisole or 0.01% all-trans retinoic acid alone have little or no activity. These results also show that the moderate depigmentation produced by the combination of 2% by weight or 1% by weight of 4-hydroxyanisole with 0.01% by weight of all-trans retinoic acid is reversible and returns to near normal color within seven weeks after discontinuing the treatment. On the other hand, 2% by weight of hydroquinone plus 0.01% by weight of all-trans retinoic acid, which showed moderate activity after eight weeks of application, failed to show any significant degree of reversibility of the depigmentation during the same time period. It is desirable to have reversible rather than permanent depigmentation since permanent depigmentation results in an unsightly area of light skin which does not recover its normal pigmentation.

B. Local Irritation

Local irritation was assessed on pig skin during the course of daily topical application of the respective agents. Comparison of the local skin irritation potential of 4-hydroxyanisole and hydroquinone with and without all-trans retinoic acid is based on the summation of Draize scores for erythema, edema and scaling. 1=minimum effect, 2=slight effect, 3=moderate to severe effect, and 4=severe effect. The maximum attainable score=12. Results are given in Table 1 and FIG. 7.

TABLE 1

Comparison of Local Skin Irritation Potential of 4-Hydroxyanisole and Hydroquinone Based on the Summation of Draize Scores for Erythema, Edema and Scaling of Skin

	Skin Irritation		
Treatment	WK 1	WK 3	WK 6
2% by weight 4-hydroxyanisole	3	0	0
2% by weight hydroquinone	3	6	4
0.01% by weight all-trans retinoic acid	3	0	2
2% by weight 4-hydroxy-	3	0	1

TABLE 1-continued

Comparison of Local Skin Irritation Potential of 4-Hydroxyanisole and Hydroquinone Based on the Summation of Draize Scores for Erythema, Edema and Scaling of Skin

Treatment	Skin Irritation WK 1	WK 3	WK 6
anisole + 0.01% by weight all-trans retinoic acid			
2% by weight hydroquinone + 0.01% by weight all-trans retinoic acid	3	6	3

It will be seen from Table 1 that 4-hydroxyanisole with and without all-trans retinoic acid elicited less irritation than hydroquinone with and without all-trans retinoic acid. Hydroquinone combined with all-trans retinoic acid and hydrocortisone was generally more irritating than hydroquinone combined with all-trans retinoic acid. It is speculated that the vasoconstrictor action of hydrocortisone causes the longer retention of hydroquinone and all-trans retinoic acid locally, leading to greater irritation.

Hence, 4-hydroxyanisole combined with all-trans retinoic acid showed less irritation and a synergistic depigmenting activity, whereas hydroquinone combined with all-trans retinoic acid was more irritating and showed similar or lower activity than hydroquinone alone. These results show that the combination of low concentrations of 4-hydroxyanisole and all-trans retinoic acid without hydrocortisone unexpectedly produce effective depigmentation with lower irritation and improved potential for inducing reversible skin depigmentation.

FIG. 7 shows that the greater depigmentation noted with 2% by weight of 4-hydroxyanisole combined with the low dose of 0.01% by weight of all-trans retinoic acid was associated with less local irritation compared to the combination of 2% by weight of hydroquinone and 0.01% by weight of all-trans retinoic acid.

In general, hydroquinone alone or combined with all-trans retinoic acid and/or hydrocortisone was more locally irritating than similar concentrations of 4-hydroxyanisole alone or combined with all-trans retinoic acid.

C. Depigmentation Activity on UVR-Induced Hyperpigmentation

Exposure of human skin to ultraviolet radiation (UVR) leads to the appearance of erythema and hyperpigmentation (tanning). In a similar manner, exposure of Yucatan minipig skin to UVR also elicits erythema followed by hyperpigmentation. The Yucatan pig skin shares many physiologic and morphologic characteristics with human skin. The thickness and general morphology of epidermis and dermis, tritiated thymidine labeling pattern and index of epidermal cells, epidermal cell turnover time and size, orientation, and distribution of vessels in skin are similar to that in humans. In view of the similarity of the pig skin to human skin, the Yucatan pig was used as a model for screening depigmenting activity on UVR induced hyperpigmentation of various compounds.

Lentigo is localized skin hyperpigmentation which is characterized by a basal melanin synthesis rate and an increased number of melanocytes at the basal level. In the treatment of solar lentigo, it is desirable to only depigment the elevated or locally stimulated hyperpigmentation and not affect normally pigmented skin around the lesion.

In the following studies, Yucatan pigs were exposed to UVR to induce hyperpigmentation. The test materials were prepared as solutions in a PEG8/ethanol vehicle comprising five parts by weight of PEG8 and 95 parts by weight of ethanol. Test solutions were applied twice daily at a dose of 2 $\mu l/cm^2$ of the flank skin. Test sites were graded on a scale of 0–4, with 4 being the maximum degree of induced hyperpigmentation and 0 representing complete depigmentation of the induced hyperpigmentation, i.e., back to the color of the normal skin.

As shown in FIG. 8, 2% by weight of 4HA combined with 0.01% by weight of TRA is significantly more active than 2% by weight of 4HA by itself and produced complete depigmentation of the UVR-induced hyperpigmented spot within eight weeks of treatment. Additionally, the depigmentation of the induced pigmentation by the combination of 4HA and TRA was apparent after the first week of treatment.

FIG. 9 shows that 2% by weight of 4HA combined with 0.01% by weight of the retinoid (N-acetyl-4-aminophenyl) retinoate is more active than 2% by weight of 4HA by itself.

FIG. 10 shows that 2% by weight of 4HA combined with 0.1% by weight of the retinoid 11-cis-13-cis-12-hydroxymethyl retinoic acid δ-lactone is more active than 2% by weight of 4HA by itself.

What is claimed is:

1. A synergistic composition for skin depigmentation which does not contain a corticosteroid and which consists essentially of from 0.1% to 5% by weight of 4-hydroxyanisole and from 0.001% to 1% by weight at least one retinoid selected from the group consisting of all-trans retinoic acid, (N-acetyl-4-amino-phenyl) retinoate and 11-cis, 13-cis-12-hydroxymethyl retinoic acid δ-lactone in a pharmaceutically acceptable topical vehicle.

2. A composition as defined in claim 1 wherein said retinoid is all-trans retinoic acid.

3. A composition as defined in claim 2 containing from 1 to 2% by weight of 4-hydroxyanisole and from 0.01 to 0.1% by weight of all-trans retinoic acid.

4. A composition as defined in claim 1 wherein said retinoid is (N-acetyl-4-aminophenyl) retinoate.

5. A composition as defined in claim 4 containing from 0.1% to 5% by weight of 4-hydroxyanisole and from 0.001% to 1% by weight of (N-acetyl-4-aminophenyl) retinoate.

6. A composition as defined in claim 5 containing from 1 to 2% by weight of 4-hydroxyanisole and from 0.01 to 0.1% by weight of (N-acetyl-4-aminophenyl) retinoate.

7. A composition as defined in claim 1 wherein said retinoid is 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone.

8. A composition as defined in claim 7 containing from 0.1% to 5% by weight of 4-hydroxyanisole and from 0.001% to 1% by weight of 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone.

9. A composition as defined in claim 8 containing from 1 to 2% by weight of 4-hydroxyanisole and from 0.01 to 0.1% by weight of 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone.

10. A method depigmenting skin which comprises topically applying to the skin a synergistic composition which does not contain a corticosteroid consisting es-

sentially of from 0.1% to 5% by weight of 4-hydroxyanisole and from 0.001% to 1% by weight at least one retinoid selected from the group consisting of all-trans retinoic acid, (N-acetyl-4-aminophenyl) retinoate and 11-cis, 13-cis-12-hydroxymethyl retinoic acid δ-lactone in a pharmaceutically acceptable topical vehicle.

11. A method as defined in claim 10 wherein said retinoid is all-trans retinoic acid.

12. A method as defined in claim 1 containing from 1 to 2% by weight of 4-hydroxyanisole and from 0.01% to 0.1% by weight of all-trans retinoic acid.

13. A method as defined in claim 10 wherein said retinoid is (N-acetyl-4-aminophenyl) retinoate.

14. A method as defined in claim 13 wherein said composition contains from 0.1% to 5% by weight of 4-hydroxyanisole and from 0.001% to 1% by weight of (N-acetyl-4-aminophenyl) retinoate.

15. A method as defined in claim 14 containing from 1 to 2% by weight of 4-hydroxyanisole and from 0.01% to 0.1% by weight of (N-acetyl-4-aminophenyl) retinoate.

16. A method as defined in claim 10 wherein said retinoid is 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone.

17. A method as defined in claim 16 wherein said composition contains from 0.1% to 5% by weight of 4-hydroxyanisole and from 0.001% to 1% by weight of 11-cis-13-cis-12-hydroxymethyl retinoic acid δ-lactone.

18. A method as defined in claim 17 containing from 1 to 2% by weight of 4-hydroxyanisole and from 0.01% to 0.1% by weight of 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone.

* * * * *

US PATENT 5194247

APPLICATION FOR EXTENSION OF PATENT TERM
UNDER 35 USC 156

APPENDIX 3

UNITED STATES DEPARTMENT OF COMMERCE
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M75N9

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MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,194,247	183	990	----	07/554,904	03/16/93	07/24/90	04	NO	PAID

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1	WW-0041A

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO: COMMISIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, D.C. 20231

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